9. (Amended) A method of treating a cell proliferative disorder associated with altered p16 expression due to methylation of a CpG island of a p16 gene in a cell, the method comprising administering to a subject with the disorder, a therapeutically effective amount of reagent which modulates expression of the p16 [expression] gene.

11. (Amended) The method of ~~claim~~ 10, wherein the reagent is [5-deoxyazacytadine] 5-deoxyazacytidine.

II. REMARKS

Claims 1 to 11 are pending. For the Examiner's convenience, a copy of the claims as they will stand upon entry of the present amendment is attached hereto as Exhibit A.

A. Regarding the Amendments

The specification has been amended to insert a substitute Sequence Listing, and to amend a Sequence Identifier such that the SEQ ID NO: corresponds to that in the substitute Sequence Listing. The substitute Sequence Listing and the amendment merely address formalities, and do not add new matter.

The specification also has been amended at page 7 to correct a readily apparent typographical error. As such, the amendment does not add new matter.

In addition, the specification has been amended at page 29 to delete reference to "mcl-1 expression" and substitute the term "such expression" to refer to the altered expression of 5'ALT or 5'ALT-p16 or -p15, which is recited earlier in the sentence. It is submitted that the

Claim 1 has been amended to more clearly indicate that a method of the invention is useful for treating a cell proliferative disorder associated with "expression of the 5'ALT polynucleotide" using a reagent that modulates "expression of the 5'ALT polynucleotide or activity of a polypeptide encoded by [the 5'ALT] polynucleotide". The amendment is supported, for example, by the paragraphs bridging pages 29 to 30 and pages 32 to 33 of the specification and, therefore, does not add new matter.

Claims 2, 3 and 4 have been amended such that the language of the claims corresponds to that of amended claim 1, from which claims 2, 3 and 4 depend. As such, the amendments merely address a formality, and do not add new matter.

Claim 9 has been amended to more clearly indicate that altered p16 expression that is associated with a cell proliferative disorder amenable to a method of treatment is "due to methylation of a CpG island of a p16 gene in a cell." The amendment is supported, for example, at page 9, third paragraph, and, therefore, does not add new matter.

Claim 11 has been amended to correct a typographical error (see, for example, page 8, line 8). As such, the amendment does not add new matter.

B. Rejection under 35 U.S.C. § 112

The rejection of claims 1 to 11 under 35 U.S.C. § 112, second paragraph, as allegedly vague and indefinite respectfully is traversed.

It is stated in the Office Action that the claimed methods are indefinite in reciting a

does not recite the term "p16 expression product" (see below), but, instead, recites the term "p16 expression".

Claim 1 has been amended to more clearly indicate that a "cell proliferative disorder" amenable to treatment using a method of the invention is one that is "associated with expression of a 5'ALT polynucleotide" and that the disorder is treated using a reagent that modulates "expression of the 5'ALT polynucleotide or activity of a polypeptide encoded by [the 5'ALT] polynucleotide." As such, it is clear from the language of amended claim 1 that a disorder "associated" with expression of a 5'ALT polynucleotide includes those disorders that involve either the 5'ALT polynucleotide or a polypeptide expressed therefrom.

It is suggested in the Office Action that the claims can encompass, for example, a disorder caused by a protein that fails to properly interact with 5'ALT such as a mutant transcription factor, and that a treatment, therefore, could involve efforts to replace the lost activation provided by such a protein or to repair the transcription factor binding site. Amended claim 1, however, requires that the disorder is "associated with expression of a 5'ALT polynucleotide." As such, a method for replacing lost activation of 5'ALT due, for example, to a mutant transcription factor or transcription factor binding site as suggested in the Office Action would not be encompassed within the claimed invention. Instead, one skilled in the art reading claim 1 would know that a method of the invention encompasses treating a cell proliferative disorder associated with expression of a 5'ALT polynucleotide either by modulating expression of the polynucleotide or by modulating the activity of a polypeptide encoded by the polynucleotide. Accordingly, it is submitted that claims 1 to 8 are clear and definite and, therefore, requested that this rejection of the claims be removed.

With respect to claims 9 to 11, it is pointed out that amended claim 9 requires that the cell proliferative disorder is "associated with altered p16 polypeptide due to methylation of a CpG island of a p16 gene in a cell." As such, it is submitted that one skilled in the art reading claim 9 clearly would know the requirements of a cell proliferative disorder amenable to treatment according to a method of the invention. Accordingly, it is requested that this ground of rejection be removed.

It is also stated, with respect to p16, that the term "product" in the limitation "expression product" is unclear. However, the term "expression product" was not present in the claims as filed, and is not present in the amended claims. Accordingly, it is respectfully requested that this ground of rejection be removed or, alternatively, that the basis for the rejection be clarified.

In summary, it is submitted that amended claims 1 to 11 clearly define the subject matter regarded as the invention such that one skilled in the art would know the metes and bounds of the claimed invention. Accordingly, it is respectfully requested that the rejection of claims 1 to 11 under 35 U.S.C. § 112, second paragraph, be removed.

The objection to the specification and corresponding rejection of claims 1 to 11 under 35 U.S.C. § 112, first paragraph, as allegedly containing lacking enablement respectfully are traversed.

It is stated in the Office Action that claims 1 to 11 encompass methods of gene therapy, but that the specification does not disclose how one readily identifies a cell proliferative disorder associated with 5'ALT and with p-16, or how to predictably treat such disorders using gene

respect to the rejection under 35 U.S.C. § 112, second paragraph, and further in view of the specification, one skilled in the art would have known how to readily identify such disorders. Applicants point out that the specification discloses, for example, that the disorders encompassed within claims 1 to 8 can be identified by detecting increased or decreased expression of 5'ALT or 5'ALT-p16 or 5'ALT-p15 (page 29, lines 9-14) using methods such as northern blot analysis (see page 32, lines 10-17). In addition, the specification discloses methods for identifying disorders encompassed within claims 9 to 11 by detecting the methylation status of a CpG island associated with a p16 gene (see paragraph bridging pages 65 to 66). Furthermore, the specification discloses that methylation of a p16 gene CpG island, for example, is associated with various human neoplasms (paragraph bridging pages 66 to 67). As such, it is submitted that one skilled in the art would have known that how to identify a cell proliferative disorder amenable to treatment according to a method of the invention, and would have known of various human neoplasms that exemplify such disorders.

With respect to gene therapy, Applicants first point out that gene therapy provides only one means for practicing a method of the invention. A method of treatment also can be performed, for example, using an antibody that binds to a polypeptide encoded by a 5'ALT polynucleotide (see, for example, amended claim 4), or using a demethlyating agent such as 5-deoxyazacytidine (see paragraph bridging pages 32 to 33; page 43, lines 8-11; see, also, claims 10 and 11). Thus, the claims encompass methods of treatment other than gene therapy.

Applicants further point out that the Stolberg article, which is cited in the Office Action in support of the position that gene therapy is unpredictable, provides several examples demonstrating the effectiveness of methods of gene therapy. For example, at page 1, the article

three hemophilia patients that have received a dose of gene therapy of Factor IX, which was so low that it was not effective in dogs, showed expression of Factor IX such that their conditions improved and their need for standard treatment was reduced (page 4). In addition, the article describes four of five babies that were born with SCID and treated by gene therapy had normal immune responses 10 months after receiving gene therapy (paragraph bridging pages 4-5). The article further describes a child with adenosine deaminase deficiency that was successfully treated using gene therapy (page 5, second full paragraph). In addition, the article describes results of a trial by Vical showing that gene therapy of advanced skin cancer patients resulted in positive results in 25% of the treated patients, a result that is remarkable due to the advanced stage of the disease and the fact that the patients had failed all other treatments (page 5, last three paragraphs). Thus, while Applicants acknowledge that those skilled in the art are cautious in expressing their optimism, it is submitted that it is clear from the Stolberg article that the skilled artisan would have known that gene therapy can be an effective method of treatment.

In summary, it is submitted that one skilled in the art, viewing the specification, would have known of cell proliferative disorders such as neoplasm that can be treated using a method of the invention, would have known how to identify other such disorders amenable to treatment according to a method of the invention, and would have known that gene therapy, for example, using antisense nucleic acid molecules, can provide one means for effecting such treatment. Accordingly, it is respectfully requested that the objection to the specification be withdrawn and that the corresponding rejection of claims 1 to 11 under 35 U.S.C. § 112, first paragraph, be removed.

C. Regarding the Sequence Listing

not filed with the subject application. However, the application as filed contained a paper copy of the Sequence Listing at pages 77 to 81, and the Transmittal Sheet filed with the application authorized use of the Sequence Listing, including CRF, of the parent application. Nevertheless, by the present amendment, it is requested that the substitute Sequence Listing, including paper copy and CRF, submitted herewith be entered into the application and, therefore, that this objection to the specification be withdrawn.

By the present amendment, Applicants comply with the requirement for an initial or substitute CRF copy of the "Sequence Listing"; an initial or substitute paper copy of the "Sequence Listing"; and a Statement that the content of the paper and computer readable copies are the same and include no new matter. The amendment to page 54 merely renumbers the sequence disclosure so that the specification corresponds with the substitute Sequence Listing. No new matter is added by the substitute Sequence Listing and amendments.

D. Regarding the Information Disclosure Statement

Applicants point out that an Information Disclosure Statement and Form 1449 were filed with the subject application. It is requested on the Form 1449 that the Examiner acknowledge consideration of the cited reference by initialing the references and returning a copy of the initialed Form 1449 to Applicants' representative. However, an initialed copy of the Form 1449 was not received. Accordingly, Applicants respectfully request the Examiner consider the references cited in the Form 1449 and return an initialed copy of the Form 1449 so indicating.

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect respectfully is requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: 11/22/00

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Enclosure: Exhibit A

EXHIBIT A

CLAIMS UPON ENTRY OF THE AMENDMENT

1. (Amended) A method of treating a cell proliferative disorder associated with expression of a 5'ALT polynucleotide, the method comprising contacting the cell having or suspected of having the disorder with a reagent which modulates expression of the 5'ALT polynucleotide or activity of a polypeptide encoded by said polynucleotide.

2. (Amended) The method of claim 1, wherein the modulation is inhibition of expression of said polynucleotide or activity of said polypeptide.

3. (Amended) The method of claim 1, wherein the modulation is stimulation of expression of said polynucleotide or activity of said polypeptide.

4. (Amended) The method of claim 1, wherein the reagent is an antibody which binds to the polypeptide encoded by said 5'ALT polynucleotide.

5. The method of claim 1, wherein the reagent is a polynucleotide.

6. The method claim 5, wherein the polynucleotide is a 5'ALT antisense sequence.

7. The method of claim 1, wherein the cell is derived from lung, pancreas, blood, head or neck.

9. (Amended) A method of treating a cell proliferative disorder associated with altered p16 expression due to methylation of a CpG island of a p16 gene in a cell, the method comprising administering to a subject with the disorder, a therapeutically effective amount of reagent which modulates expression of the p16 gene.

10. The method of claim 9, wherein the reagent is a demethylating agent.

11. (Amended) The method of claim 10, wherein the reagent is 5-deoxyazacytidine.